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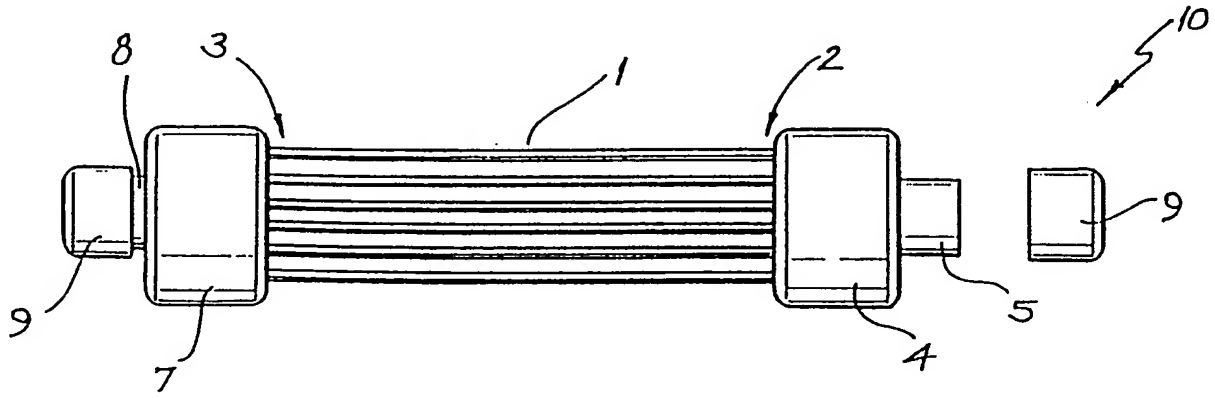

(57) Abstract

The invention relates to an implantable device for keeping transplanted cells alive *in vivo*, in an animal. The device comprises: at least one thin walled, hollow, cell closeable, semi-permeable tube, having an internal diameter appropriate to enable cells within the tube to remain functionally viable, and a large pore hydrophobic membrane wall of appropriate thickness, inducing vascularisation on implanting thereby permitting nutrient and metabolite transfer between body fluids surrounding the tube and the cells, providing an immune barrier between the cells and the body fluids, and enabling the cells within the tube to remain viable. Methods of implanting the device are also provided, whereby vascularisation of the exterior of the device is achieved *in vivo* before or after instillment of the viable cells into the device. The implanted device can be used to provide animals with transplanted viable cells *in vivo* which secrete a substance required by the animal or which metabolise a substance in the animal.

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IMPLANTABLE DEVICE

Technical Field

The present invention relates to an implantable device for keeping transplanted cells alive *in vivo*, and to methods of implanting such a device, whereby vascularisation of the exterior of the device is achieved *in vivo*, before or after instilment of the living cells into the device. The invention also relates to methods of treating animals comprising implantation of the device containing selected cells, or the subsequent instilment of selected cells into the empty device after vascularisation has occurred.

Background Art

Endocrine deficiency diseases are currently treated with hormone replacement therapy. The therapeutic regimens employed range from multiple daily injections or oral therapy to implants that provide a steady hormone level over months. While this mode of therapy maintains an improved quality of life over the untreated disease state, it is not equivalent to the normal state where an organ maintains relative homeostasis in the individual by supplying a hormone in response to a sensed, variable metabolic need. Current inability to produce artificial infusion devices that can mimic normal endocrine organ function has motivated research efforts to transplant endocrine organs or their essential cellular elements into deficient individuals.

Human organ transplant recipients generally require life-long immunosuppression to prevent immune rejection of the organ. The undesirable side effects of current immunosuppressive agents are outweighed by the individual's need for major organ transplants, such as heart, lung, liver or kidney. However, because the morbidity and mortality associated with those side effects may be worse than those which endocrine deficiency patients experience with conventional therapy, alternate means are being sought to prevent immune attack on transplanted endocrine organs.

One such alternative, called immunoisolation, surrounds the transplanted organ, or its essential elements, with a physical barrier that is impermeable to the active molecules and cells of the immune system, but is permeable to nutrients, the hormone(s) secreted by that organ, and the metabolite(s) that trigger the release of the hormone(s). Extant immunoisolation devices can be divided into vascular and extravascular types.

Vascular devices generally contain endocrine cells in a chamber surrounding artificial blood vessels, wherein the vessel walls serve both as an immune barrier and as an extension of the circulatory system. The advantage of vascular devices is the proximity of the endocrine cells to the blood, which permits adequate access to nutrients and oxygen, and shortens the time for the cells to receive a metabolic stimulus and deliver the hormone response into the circulation. Vascular devices have been unsuccessful because blood clotting could not be prevented on the blood contacting surfaces.

Extravascular devices contain endocrine cells in a chamber bounded by an immune barrier membrane. The cells depend on molecules diffusing from adjacent blood vessels through tissues, body fluids and the limiting membrane to supply their nutrients and oxygen, and to sense the concentration of the metabolites that trigger their secretory response. In turn the secreted hormone must diffuse back through the limiting membrane, body tissues and then body fluids to reach the circulatory system.

It follows that the proximity of capillary beds to the semipermeable membrane surface of an implanted hybrid organ becomes a critical factor in two essential processes: a) whether the endocrine cells receive sufficient oxygen and nutrients to live and function normally, and b) whether the time required for a hormone to be delivered into the circulatory system in response to a metabolite change is short enough to maintain the normal homeostasis. Design of a device that rigorously mimics the anatomy of natural endocrine organs would require that all cells be positioned within about 10 - 20 micrometers from a blood capillary. For example, islets of Langerhans, the active elements of the endocrine pancreas, average about 150 micrometers in diameter and typically contain 3 - 5,000 cells, and are intensely vascularised such that any cell is within 2 cell diameters from a capillary. It follows, that an artificial device containing intact islets, even when the surface of each islet is closely invested by a capillary network, does not provide as short a diffusion path as the native islet environment.

Current and previous extravascular devices are thought to have failed because they were not designed to maintain their contained cells sufficiently close to a blood supply. Some designs packed endocrine cells into a semipermeable tube having an internal diameter of about 1000 micrometers, which typically caused death or malfunction of those cells

nearer the center (more distant from the wall). Other designs placed small 150-200 micrometer clumps of cells inside spherical microcapsules of 500-800 micrometer diameter. Under such conditions the cells would be far from the surface through which nutrients and metabolites must diffuse and the surface itself would be far from capillary beds.

Extravascular devices are also thought to have failed because their surface initiated a foreign body response by the surrounding tissue. Foreign body responses typically establish a thick and dense fibrous capsule, relatively devoid of blood vessels, around the implanted material. This capsule is thought to seriously retard diffusion of essential nutrients, metabolites and hormones between the device and blood vessels, whether by distance effects or by diffusive resistance of the fibrous capsule. The establishment of this fibrous capsule is causally related to recognition of the foreign implant by macrophages. Stimulated macrophages attempt to digest the surface of the implant by releasing enzymes and toxins at its surface. It is believed to be advantageous for endocrine cells within the implant to avoid the release of such toxic material in their near vicinity, since they may also be damaged by these agents.

Objects of the invention

It is therefore an object of the invention to provide a device capable of maintaining viable transplanted cells *in vivo*.

It is a further object of the invention to provide methods of implanting such a device in an animal.

Another object of the invention is to provide methods of treating disorders such as endocrine hormone deficiency states in an animal.

Disclosure of the Invention

The present invention derives from the entirely unexpected finding that living cells may be transplanted into the body and maintained in a functionally viable state in an implantable device according to the invention. The empty device is initially implanted in an animal and left to allow vascularisation of the exterior of the device to occur. A substantial number of viable cells can then be instilled into the device *in vivo* some time after original implantation of the device, without contamination of the instilled cells. Alternatively the device may be pre-filled with selected viable cells prior to implantation. In either case the cells may later be emptied and the device replenished *in situ*.

The size and integrity of the device allows it to be stably located in the body by a surgeon and be maintained as a recoverable entity.

Thus according to a first embodiment of the invention there is provided, an implantable device for keeping transplanted cells alive in vivo, in an animal, comprising:

at least one thin walled, hollow, cell closeable, semi-permeable tube having:

an internal diameter appropriate to enable cells within the tube to remain functionally viable; and

a large pore hydrophobic membrane wall of appropriate thickness, inducing vascularisation on implanting thereby permitting nutrient and metabolite transfer between body fluids surrounding the tube and the cells, providing an immune barrier between the cells and the body fluids, and enabling the cells within the tube to remain viable.

The length of the tubes will vary according to their other dimensions such as wall thickness and internal diameter and also according to the cell type and implantation site within the body. Advantageously, tubes of about 30cm in length are employed.

The device may further comprise means to close the tube, which may be in the form of a plug, a cap, a clamp or the like.

In accordance with a second embodiment of the invention there is provided an implantable device for keeping transplanted cells alive in vivo, in an animal, comprising:

a plurality of thin walled, hollow, cell closeable, semi-permeable tubes, each tube having a first and a second end and having:

an internal diameter appropriate to enable cells within the tube to remain functionally viable;

a large pore hydrophobic membrane wall of appropriate thickness, inducing vascularisation on implanting thereby permitting nutrient and metabolite transfer between body fluids surrounding the tube and the cells, providing an immune barrier between the cells and the body fluids, and enabling the cells within the tube to remain viable;

a first support operatively associated with the first ends of said tubes having a closeable entrance;

a second support operatively associated with the second ends of said tubes having a closeable exit;

the closeable entrance and exit permitting filling of the tubes with selected viable cells.

This form of the invention generally includes means to close the entrance and exit which typically are in the form of first and second closure caps for closing the entrance and exit respectively.

The length and number of the tubes will vary according to the volume of cells required, and other factors such as implantation site and access to the systemic circulation. Generally 3 to 12 tubes are present, the length of the tubes varying between about 3 to about 30 cm. Advantageously 4 or 5 tubes of approximately 10cm in length are employed.

The first and second ends of the tubes may be manifolded so as to communicate with the respective exit and entrance of the device. In one form the entrance and exit may communicate with chambers inside the first and second supports respectively which in turn communicate with the first and second ends of the tubes. Alternatively the tubes are drawn together at the first and second ends to fit within the entrance and exit respectively.

According to a third embodiment of the invention there is provided an implantable device for keeping transplanted cells alive in vivo, in an animal, comprising:

a plurality of thin walled, hollow, cell closeable, semi-permeable tubes, each tube having a first and a second end and having:

an internal diameter appropriate to enable cells within the tube to remain functionally viable;

a large pore hydrophobic membrane wall of appropriate thickness, inducing vascularisation on implanting thereby permitting nutrient and metabolite transfer between body fluids surrounding the tube and the cells, providing an immune barrier between the cells and the body fluids, and enabling the cells within the tube to remain viable;

the first ends of said tubes communicating with a closeable entrance thereby permitting filling and closure of the tubes; and

a support operatively associated with the tubes, for holding at least a portion of the tubes in proximal relationship with each other.

Desirably the components of the device are constructed of, or are coated with, bio-compatible materials such as medical implant grade silicone rubber, polyethylene, polypropylene, cuprophane, polyacrylonitrile or teflon to protect against a foreign body response being mounted against the implant.

In the practice of the invention small diameter thin walled hollow-tubes are used to provide shorter diffusion paths between the blood vessels outside the wall and all the cells inside the tube.

The hollow tubes are constructed of a large pore hydrophobic semi-permeable material, which is capable of encapsulating the living cells and of inducing vascularisation to occur about the tube on implanting in the body of any animal. Thus allowing transfer of nutrients and desired compounds or elements required to trigger a desired response by cells, into the cells, and secreted products from the implanted cells. Suitable materials therefore are those having a pore-size generally greater than about 150,000 daltons, (i.e. greater than about 0.005µm), such as appropriate grades of polyethylene, polypropylene or polyacrylonitrile. Goretex (Registered Trade Mark) may also be used. Generally the pore size of the material is in the range of about 0.005 µm to 1.0 µm, typically from about 0.05 µm to about 0.6 µm with a pore size of 0.5 µm being desirable.

The lower limit of pore size is related to the dimension of wall thickness in that the thinner the wall of the tube, the smaller the pore size can be. Thus, pore sizes less than 150,000 daltons should be achievable with tubes having appropriately thin walls. The upper limit of pore dimensions should be less than those which permit transfer of undesirable contaminants from the blood into the tube. The biocompatibility of the material from which the tube is made is also a factor.

The tubes may be coated with biocompatibility-enhancing substances such as fibronectin, laminin, or collagen, and/or be coated with a biodegradable gel containing corticosteroids or other drugs that regulate the formation of fibrotic tissue around the device.

The internal dimensions of a tube should be no greater than those which permit adequate nutrient transfer between blood capillaries surrounding the tube and cells within the tube so that the cells remain viable <u>in vivo</u>.

Desirably the wall thickness of the tubes is less than about 100µm, typically from about 45 µm to about 95 µm, and their internal diameter is generally from about 20 µm to 1 mm, typically from about 200 µm to about 500 µm.

Generally the support(s) will be in the form of a block of silicone rubber or other suitable material into which the tubes are embedded.

Alternatively the support may comprise any appropriate means of holding the tubes together such as a band or ligature or a suitable housing.

Typically the tubes on implantation in the body are closed to the entry of external cells at both ends by means of a cap, plug, or filter, or other suitable closure means, which are removable to allow instilment of cells.

According to a fourth embodiment of the invention there is provided a method of implanting a device of the first embodiment in an animal comprising:

implanting the device in the animal under aseptic conditions, with the tube of the device closed to intrusion by external cells;

leaving the device in the animal whereby vascularisation occurs about the tube;

filling the tube of the implanted device under aseptic conditions with selected viable cells ; and

closing the tube of the implanted device under aseptic conditions.

According to a fifth embodiment of the invention there is provided a method of implanting a device of the second or third embodiment in an animal comprising:

implanting the device in the animal under asceptic conditions with the tubes closed to intrusion by external cells;

leaving the device in the animal whereby vascularisation occurs about the tubes;

filling the tubes of the implanted device under asceptic conditions with selected viable cells; and

closing the tubes under asceptic conditions.

According to a sixth embodiment of this invention there is provided a method of implanting a device of the first embodiment, in an animal comprising:

filling the tube of the device with selected viable cells under aseptic conditions;

closing the tube under aseptic conditions;

implanting the device in an animal under aseptic conditions; and

leaving the implanted device in the animal whereby vascularisation occurs about the tube.

According to a seventh embodiment of the invention there is provided a method of implanting a device of the second or third embodiment in an animal comprising:

filling the tubes of the device with selected viable cells under asceptic conditions;

closing the tubes under asceptic conditions;

implanting the device in an animal under asceptic conditions; and

leaving the implanted device in the animal whereby vascularisation occurs about the tubes.

Optionally in a further step the implanted device may be emptied and refilled with cells.

The exit of the device may be adapted to attach to a vacuum pump so that on attachment of the device to the pump a vacuum is created inside the tube to facilitate filling of the tube with the selected cells. The pressure inside the tube being controlled by means of a valve connected with the pump.

Typically the device is implanted into highly vascularised host tissue e.g., a surgically-formed pouch (fold) in the omentum or into subcutaneous or other adipose tissue. It is anticipated that the device may also be implanted and/or filled percutaneously under radiological control or other means, or that one end of a tube of the device can be left in communication with the external surface of the animal's body and be filled externally without the need for further invasive procedures.

In practice the steps of implantation and instilment of cells into the device are carried out under as strict aseptic conditions as possible in order to prevent contamination of the inside of the tube, and cells contained therein.

To enhance the vascularisation process, the exterior of the hollow tubes may be coated with angiogenic factors, or a biodegradable gel containing angiogenic factors, which are capable of enhancing capillary growth proximate to the external surface of the tubes. Suitable angiogenic factors include slow release heparin, platelet derived growth factor, epidermal growth factor, or cis-hydroxyproline.

According to an eighth embodiment of this invention there is provided

a method of providing an animal with transplanted viable cells <u>in vivo</u> which secrete a substance required by the animal, which method comprises:

implanting a device according to the first embodiment into the animal in accordance with the method of the fourth or sixth embodiment; and

wherein the tube is filled with a quantity of selected viable cells which secrete an effective amount of the substance.

According to a ninth embodiment of the invention there is provided a method of providing an animal with transplanted viable cells in vivo which secrete a substance required by the animal, which method comprises:

implanting a device according to the second or third embodiment into the animal in accordance with the method of the fifth or seventh embodiment; and wherein the tubes are filled with a quantity of cells which secrete an effective amount of the substance.

In particular the invention provides a method of treating an animal with an endocrine hormone deficiency state, wherein the selected cells are capable of producing at least one appropriate endocrine hormone.

In practice the method of treatment is particularly important in the therapy of pancreatic deficiency states, such as deficiency of the pancreatic hormone insulin in Diabetes Mellitus. However, the treatment of deficiency states due to the absence or failure of other endocrine organs such as the thyroid, adrenals, pituitary, ovaries or testes, is also within the scope of the present invention.

Where a deficiency state involves more than one hormone such as in generalised pituitary failure, it is possible to instill more than one cell type producing the appropriate hormone into an individual tube or alternatively different cell types may be inserted into different tubes in the same device or into separate devices, for implantation in the animal.

The effective number of cells of a selected cell type required will obviously vary according to the particular deficiency state and its severity, and according to the age, sex, weight, general condition, etc of the patient and other variables affecting the clinical state such as intercurrent illnesses. In addition the site of implantation in the body will also influence the number of cells required, due to factors such as distance from target organ and degree of access to the systemic circulation.

According to a tenth embodiment of this invention there is provided a method of providing an animal with transplanted viable cells in vivo which metabolise a substance in the animal, which method comprises:

implanting a device according to the first embodiment into the animal in accordance with the method of the fourth or sixth embodiment; and

wherein the tube is filled with a quantity of selected viable cells which metabolise an effective amount of the substance.

According to a eleventh embodiment there is provided a method of providing an animal with transplanted viable cells in vivo which metabolise a substance in the animal, which method comprises:

implanting a device according to the second or third embodiment into the animal in accordance with the method of the fifth or seventh embodiment, and wherein the tubes are filled with a quantity of selected viable cells which metabolise an effective amount of the substance.

Substances to be metabolised include metabolites or waste products produced by the animal, or externally derived toxins, which the animal is incapable of dealing with effectively itself, and which would be harmful to the animal if allowed to accumulate.

The invention also includes within its scope methods of sensing the presence of, or monitoring the concentration of, compounds or elements within the body of an an animal. Such methods may be used in the diagnosis or monitoring of disease or deficiency states.

In this case the selected cells implanted according to the invention, are capable of responding to or reacting with an appropriate compound, element, or condition and of producing a detectable entity.

The compound or element may be a hormone, an enzyme, an enzyme cofactor, an antigen, an antibody, a metabolite, a toxin, a vitamin, a protein, a trace element, and a gas, for example. The detectable entity may be a metabolic product detectable in the blood or urine, or an alteration in cell membrane potential, detected by suitable sensing means. The signal may be quantitatively measured where the compound or element is being monitored over a given time period.

The methods of the invention are applicable to all animals, and are especially useful in the treatment of humans and mammals generally.

The cells used in the practice of the invention are typically taken from an animal of the same species as the recipient, or of a different species, or the cells may be obtained from special cell lines or from tissue culture. Alternatively it would be possible to use autologous cells, which have been taken from the recipient animal and stored under appropriate conditions, and/or cultured <u>in vitro</u>, before reimplantation according to the invention.

The device according to the invention overcomes many of the enumerated problems of prior art devices. Previous literature on both microcapsule and hollow fibre systems, seems to point to the use of fibres of inappropriate wall thickness, internal diameter, and pore size. In particular, materials with large pore size were avoided since it was thought prior to the present invention that such materials would allow the

entry of antibodies into the interior of the device resulting in destruction of the cells. The inventors have found a number of advantages in using a large pore size membrane, namely: that large pore size membranes are easier to fabricate, they allow easier passage of large molecular weight nutrients (e.g. large fatty acids) from the blood stream to the implanted cells and also they may be less effected by clogging with protein and other body substances.

Previous hollow fibre devices have used pre-filled single fibres which did not provide a large enough mass of cells to be really effective. Furthermore, in the past, thick walled, large internal diameter hollow fibres have been used for encapsulation. These have the disadvantage of providing very long nutrient diffusion paths to the implanted cells, particularly cells at the centre of the fibres, which often died or at least were not healthy functioning cells.

Thus the present device is the first device that both contains enough viable cells to be effective and more significantly allows a mechanism for instilling cells into the tubes some time after implantation and after vascularised tissue has grown around the tubes.

In addition the shape of the present device allows for firm anchorage both by the surgeon being able to suture the semi-rigid ends to host tissue as well as through the device obtaining firm anchorage through tissue ingrowth around and between the multiple hollow fibres. This has not been achieved with previous devices which have just used isolated hollow fibres. Also, the single integrated entity structure allows easy location and removal of the device if there are problems. This is much harder with single hollow fibres and impossible with implanted islet microcapsule systems.

The device of the invention has the following additional advantages:

1. A tube of the device acts as an immune barrier that allows free passage of essential nutrients, oxygen and the secreted hormones, but is impermeable to active elements of the immune system.
2. The thickness of a tube of the device in effect minimizes the distance between any one cell contained inside the barrier and adjacent blood capillaries outside the barrier.
3. The device is capable of causing blood capillaries to form and remain near the surface of the immune barrier prior to, or after, instilment of cells inside the device.

4. The device avoids establishment of a thick, dense fibrous capsule relatively devoid of blood vessels at the surface of the implant.

Brief description of the drawing

A preferred form of the present invention will now be described by way of example with reference to the accompanying drawings, wherein:

Figure 1 illustrates a schematic top plan view of a device of the invention.

Figure 2 illustrates a schematic top plan view of an alternative device of the invention.

Best mode for carrying out the invention

The Figures illustrate preferred embodiments of the device according to the invention. Although 6 tubes are shown for the purpose of illustration the number of tubes can be varied as required as may the length of the tubes.

Device 10 consists of multiple hollow tubes 1 having first ends 2 and second ends 3. First ends 2 of hollow tubes 1 are operatively associated with first support 4. First support 4, has a closeable entrance 5 for filling tubes 1 with cells, into which first ends 2 of tubes 1 are inserted. Entrance 5 is reduced in size to fit a standard Record lock syringe. Second ends 3 of tubes 1 are operatively associated with second support 7. Second support 7 has a closeable exit 8, into which second ends 3 of tubes 1 are inserted, permitting the filling of tubes 1 with cells via entrance 5. Hollow tubes 1 are composed of a polyethylene or polypropylene semi-permeable membrane material that elicits minimal foreign body response in the host and resists build-up of fibrotic tissue on the exterior surface, with a pore size of about 0.5μm, wall thickness of about 90μm and internal diameter about 330μm. First support 4 and second support 7 may be composed of any appropriate potting substance such as epoxy resin, which may then be coated with a more biocompatible substance such as medical implant grade silicone rubber to render it more inert. Entrance 5 and exit 8 at each extremity of device 10 have removable caps 9, caps 9 being constructed of or coated with a biocompatible substance such as silicone rubber. Between first ends 2, and second ends 3, hollow tubes 1 are left free so that vascular and connective tissue can grow around and between them to provide nutrients to, and allow passage of secreted products from, the encapsulated cells.

Implantation of device 10 is a two-stage procedure carried out under strict aseptic conditions. The first stage is to implant empty device 10, which may or may not be pretreated, externally and/or internally with biocompatibility-enhancing factors such as fibronectin, and/or externally with angiogenic factors such as slow release heparin, into subcutaneous tissue of the recipient. When vascular and connective tissue has grown around device 10, the second stage is performed. This involves carefully removing both of caps 9 from entrance 5 and exit 8, of device 10 and aseptically loading hollow tubes 1 of device 10 with selected cells via entrance 5, by means of a standard Record lock syringe. To facilitate filling of hollow tubes 1, exit 8 may be connected to vacuum pump 11 by means of conduit 12. On operation of vacuum pump 11 a vacuum is created in hollow tubes 1 prior to loading with selected cells via entrance 5. The pressure in hollow tubes 1 is controlled by valve 13 connected to vacuum pump 11. Caps 9 are then reinserted either as a friction fit or with the aid of a sealant or glue.

In preparation for instilment in device 10, the selected cells are isolated from suitable tissue by enzymatic digestion and purification procedures known in the art, to obtain as pure a cell preparation as possible, free from unwanted cells and other contaminants.

In implantation experiments in mice, the above device has been shown to elicit a minimal fibrotic response and not to discourage the growth of vascular tissue close to the tubes. A tube internal diameter of 330μm and wall thickness of 90μm has proved satisfactory to maintain viability of implanted pancreatic islet cells in mice for up to 60 days. However it is anticipated that a thinner walled hollow tube should be better.

Alternatively, implantation of device 10 is carried out in a single step under strict aseptic conditions. This involves carefully removing both of caps 9 from entrance 5 and exit 8, of device 10 and aseptically loading hollow tubes 1 of device 10 with selected cells via entrance 5, by means of a standard Record lock syringe. In preparation for instilment in device 10, the selected cells are isolated from suitable tissue by enzymatic digestion and purification procedures known in the art, to obtain as pure a cell preparation as possible, free from unwanted cells and other contaminants. To facilitate filling of hollow tubes 1, exit 8 may be connected to vacuum pump 11 by means of conduit 12. On operation of vacuum pump 11 a vacuum is created in hollow tubes 1 prior to loading with

selected cells via entrance 5. The pressure in hollow tubes 1 is controlled by valve 13 connected to vacuum pump 11. Caps 9 are then reinserted either as a friction fit or with the aid of a sealant or glue. The filled device 10, which may or may not be pretreated, externally and/or internally with biocompatibility-enhancing factors such as fibronectin, and/or externally with angiogenic factors such as slow release heparin, is then aseptically implanted into subcutaneous tissue of the recipient. Vascular and connective tissue then grow around device 10, to supply the cells with essential nutrients.

Industrial Applicability

The device of the present invention will find wide application in the medical and veterinary fields.

Although the foregoing description is oriented towards a biohybrid artificial pancreas containing pancreatic islet cells, it will be obvious that the device and method can be applied to any transplanted cell types which need to be implanted extra-vascularly but in close communication with the circulatory system.

IMPLANTABLE DEVICE

CLAIMS

1. An implantable device for keeping transplanted cells alive *in vivo*. in an animal comprising:

at least one thin walled, hollow, cell closeable, semi-permeable tube having;

an internal diameter appropriate to enable cells within the tube to remain functionally viable; and

a large pore hydrophobic membrane wall of appropriate thickness, inducing vascularisation on implanting thereby permitting nutrient and metabolite transfer between body fluids surrounding the tube and the cells, providing an immune barrier between the cells and the body fluids, and enabling the cells within the tube to remain viable.

2. The device of claim 1 wherein the membrane wall has a pore size greater than about 0.005 μm.

3. The device of claim 2 wherein the pore size is from about 0.005 μm to about 1.0 μm.

4. The device of claim 2 wherein the pore size is from about 0.05 μm to about 0.6 μm.

5. The device of claim 1 wherein the thickness of the membrane wall is from about 20 μm to about 100 μm.

6. The device of claim 5 wherein the thickness of the membrane wall is from about 45 μm to about 95 μm.

7. The device of claim 1 wherein the tube has an internal diameter of about 20 μm to about 1 mm.

8. The device of claim 7 wherein the tube has an internal diameter of about 200 μm to about 500 μm.

9. The device of claim 1 wherein the tube is coated with at least one biocompatibility enhancing substance.

10. The device of claim 9 wherein the biocompatibility enhancing substance is selected from the group consisting of: fibronectin, laminin and collagen.

11. The device of claim 1 wherein the tube is coated with a biodegradable gel containing at least one agent capable of regulating the formation of fibrous tissue around the device.

12. The device of claim 11 wherein the agent is a corticosteroid.

13. The device of claim 1 wherein the tube is coated with at least one angiogenic factor.

14. The device of claim 13 wherein the angiogenic factor is selected from the group consisting of: slow release heparin, platelet derived growth factor, epidermal growth factor and cis-hydroxyproline.

15. The device of claim 1 further comprising means to close the tube.

16. The device of claim 15 wherein the means is selected from the group consisting of: a clamp, a plug, and a cap.

17. An implantable device for keeping transplanted cells alive in vivo, in an animal, comprising:

a plurality of thin walled, hollow, cell closeable, semi-permeable tubes, each tube having a first and a second end and having:

an internal diameter appropriate to enable cells within the tube to remain functionally viable;

a large pore hydrophobic membrane wall of appropriate thickness, inducing vascularisation on implanting thereby permitting nutrient and metabolite transfer between body fluids surrounding the tube and the cells, providing an immune barrier between the cells and the body fluids, and enabling the cells within the tube to remain viable;

a first support operatively associated with the first ends of said tubes having a closeable entrance;

a second support operatively associated with the second ends of said tubes having a closeable exit;

the closeable entrance and exit permitting filling of the tubes with selected viable cells.

18. The device of claim 17 wherein the membrane walls have a pore size greater than about 0.005 μm.

19. The device of claim 18 wherein the pore size is from about 0.005 μm to about 1.0 μm.

20. The device of claim 18 wherein the pore size is from about 0.05 μm to about 0.6 μm.

21. The device of claim 17 wherein the thickness of each of the membrane walls is from about 20 μm to about 100 μm.

22. The device of claim 21 wherein the thickness of each of the membrane walls is from about 45 μm to about 95 μm.

23. The device of claim 17 wherein each of the tubes has an internal diameter of about 20 μm to about 1 mm.

24. The device of claim 23 wherein each of the tubes has an internal diameter of about 200 μm to about 500 μm.

25. The device of claim 17 wherein each of the tubes are coated with at least one biocompatibility enhancing substance.

26. The device of claim 25 wherein the biocompatibility enhancing substance is selected from the group consisting of: fibronectin, laminin and collagen.

27. The device of claim 17 wherein each of the tubes are coated with a biodegradable gel containing at least one agent capable of regulating the formation of fibrous tissue around the device.

28. The device of claim 27 wherein the agent is a corticosteroid.

29. The device of claim 17 wherein each of the tubes are coated with at least one angiogenic factor.

30. The device of claim 29 wherein the angiogenic factor is selected from the group consisting of: slow release heparin, platelet derived growth factor, epidermal growth factor and cis-hydroxyproline.

31. The device of claim 17 further comprising means to close the entrance and exit.

32. The device of claim 31 wherein the means comprises first and second closure caps for closing the entrance and the exit respectively.

33. The device of claim 17 comprising 2 to 12 tubes.

34. The device of claim 17 wherein each of the tubes are from about 3 cm to about 30 cm in length.

35. The device of claim 34 wherein each of the tubes are about 10 cm in length.

36. The device of claim 17 wherein the device comprises a biocompatible material.

37. The device of claim 36 wherein the biocompatible material is selected from the group consisting of: medical implant grade silicone rubber, polyethylene, polypropylene, cuprophane, polyacrylonitrile and teflon.

38. The device of any one of claims 1 to 3 or 17 to 19 wherein each of the membrane walls is formed of a material selected from the group consisting of: polyethylene, polypropylene and polyacrylonitrile.

39. An implantable device for keeping transplanted cells alive <u>in vivo</u>, in an animal, comprising:

a plurality of thin walled, hollow, cell closeable, semi-permeable tubes, each tube having a first and a second end and having:

an internal diameter appropriate to enable cells within the tube to remain functionally viable;

a large pore hydrophobic membrane wall of appropriate thickness, inducing vascularisation on implanting thereby permitting nutrient and metabolite transfer between body fluids surrounding the tube and the cells, providing an immune barrier between the cells and the body fluids, and enabling the cells within the tube to remain viable;

the first ends of said tubes communicating with a closeable entrance thereby permitting filling and closure of the tubes; and

a support operatively associated with the tubes, for holding at least a portion of the tubes in proximal relationship with each other.

40. A method of implanting the device of claim 1 in an animal comprising:

implanting the device in the animal under asceptic conditions, with the tube of the device closed to intrusion by external cells;

leaving the device in the animal whereby vascularisation occurs about the tube;

filling the tube of the implanted device under asceptic conditions with selected viable cells; and

closing the tube of the implanted device under asceptic conditions.

41. A method of implanting the device of claim 1 in an animal comprising:

filling the tube of the device under asceptic conditions with selected viable cells;

closing the tube under asceptic conditions;

implanting the device in an animal under asceptic conditions; and

leaving the implanted device in the animal whereby vascularisation occurs about the tube.

42. A method of providing an animal with transplanted viable cells <u>in vivo</u> which secrete a substance required by the animal, which method comprises:

implanting the device of claim 1 in the animal under asceptic conditions with the tube of the device closed to intrusion by external cells;

leaving the device in the animal whereby vascularisation occurs about the tube;

filling the tube of the implanted device under asceptic conditions with a quantity of selected viable cells which secrete an effective amount of the substance; and

closing the tube of the implanted device under asceptic conditions.

43. A method of providing an animal with transplanted viable cells in vivo which secrete a substance required by the animal, which method comprises:

filling the tube of the device of claim 1 under asceptic conditions with a quantity of selected viable cells which secrete an effective amount of the substance;

closing the tube under asceptic conditions;

implanting the device in the animal under asceptic conditions; and

leaving the implanted device in the animal whereby vascularisation occurs about the tube.

44. A method of providing an animal with transplanted viable cells in vivo which metabolise a substance in the animal, which method comprises:

implanting the device of claim 1 in the animal under asceptic conditions with the tube of the device closed to intrusion by external cells;

leaving the device in the animal whereby the vascularisation occurs about the tube;

filling the tube of the implanted device under asceptic conditions with a quantity of selected viable cells which metabolise an effective amount of the substance; and

closing the tube of the implanted device under asceptic conditions.

45. A method of providing an animal with transplanted viable cells in vivo which metabolise a substance, which method comprises:

filling the tube of the device of claim 1 under asceptic conditions with a quantity of selected viable cells which metabolise an effective amount of the substance;

closing the tube under asceptic conditions;

implanting the device in the animal under asceptic conditions; and

leaving the implanted device in the animal whereby vascularisation occurs about the tube.

46. The method of any one of claims 40 to 45 wherein the wall of the tube has a pore size greater than about 0.005 μm.

47. The method of claim 42 or 43 wherein the animal has an endocrine hormone deficiency state, and the selected cells are capable of producing at least one appropriate endocrine hormone.

48. The method of claim 42 or 43 wherein the animal suffers from Diabetes Mellitus and the selected cells are pancreatic islet cells.

49. The method of claim 44 or 45 wherein the substance to be metabolised is selected from the group consisting of: metabolites produced by the animal, waste products produced by the animal, and externally derived toxins.

50. A method of implanting the device of claim 17 in an animal comprising:

implanting the device in the animal under asceptic conditions with the tubes closed to intrusion by external cells;

leaving the device in the animal whereby vascularisation occurs about the tubes;

filling the tubes of the implanted device under asceptic conditions with selected viable cells; and

closing the tubes under asceptic conditions.

51. A method of implanting the device of claim 17 in an animal comprising:

filling the tubes of the device under asceptic conditions with selected viable cells;

closing the tubes under asceptic conditions;

implanting the device in an animal under asceptic conditions; and

leaving the implanted device in the animal whereby vascularisation occurs about the tubes.

52. A method of providing an animal with transplanted viable cells in vivo which secrete a substance required by the animal, which method comprises:

implanting the device of claim 17 in the animal under asceptic conditions with the tubes closed to intrusion by external cells:

leaving the device in the animal whereby the vascularisation occurs about the tubes;

filling the tubes of the implanted device under asceptic conditions with a quantity of selected viable cells which secrete an effective amount of the substance; and

closing the tubes under asceptic conditions.

53. A method of providing an animal with transplanted viable cells in vivo which secrete a substance required by the animal, which method comprises:

filling the tubes of the device of claim 17 under asceptic conditions with a quantity of selected viable cells which secrete an effective amount of the substance;

closing the tubes under asceptic conditions;

implanting the device in the animal under asceptic conditions; and

leaving the implanted device in the animal whereby vascularisation occurs about the tubes.

54. A method of providing an animal with transplanted viable cells in vivo which metabolise a substance in the animal which method comprises:

implanting the device of claim 17 in the animal under asceptic conditions with the tubes closed to intrusion by external cells;

leaving the device in the animal whereby vascularisation occurs about the tubes;

filling the tubes of the implanted device under asceptic conditions with a quantity of selected viable cells which metabolise an effective amount of the substance; and

closing the tubes of the implanted device under asceptic conditions.

55. A method of providing an animal with transplanted viable cells in vivo which metabolise a substance in the animal, which method comprises:

filling the tubes of the device of claim 17 under asceptic conditions with a quantity of selected viable cells which metabolise an effective amount of the substance;

closing the tubes under asceptic conditions;

implanting the device in the animal under asceptic conditions; and

leaving the implanted device in the animal whereby vascularisation occurs about the tubes.

56. The method of any one of claims 50 to 55 wherein the wall of each tube has a pore size greater than about 0.005 μm.

57. The method of claim 52 or 53 wherein the animal has an endocrine hormone deficiency state, and the selected cells are capable of producing at least one appropriate endocrine hormone.

58. The method of claim 52 or 53 wherein the animal suffers from Diabetes Mellitus and the selected cells are pancreatic islet cells.

59. The method of claim 54 or 55 wherein the substance to be metabolised is selected from the group consisting of: metabolites produced by the animal, waste products produced by the animal, and externally derived toxins.

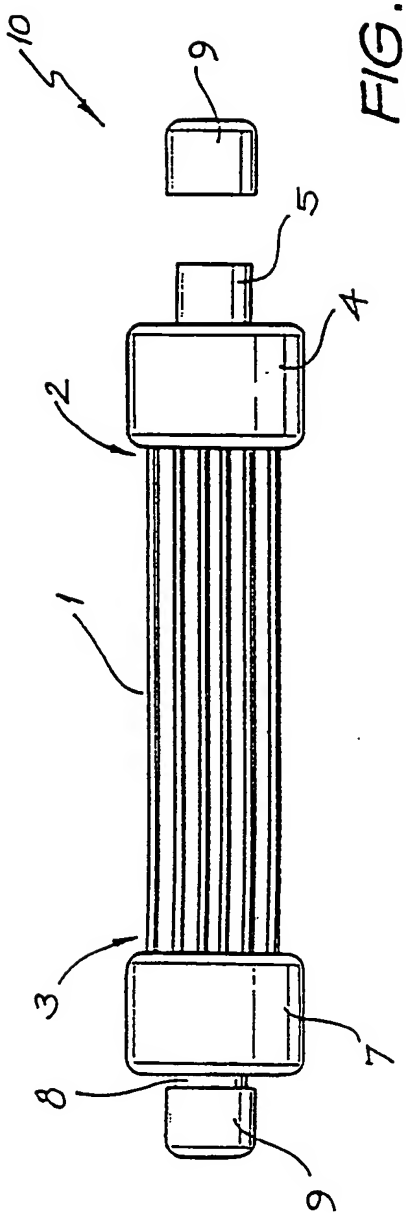

FIG. 1

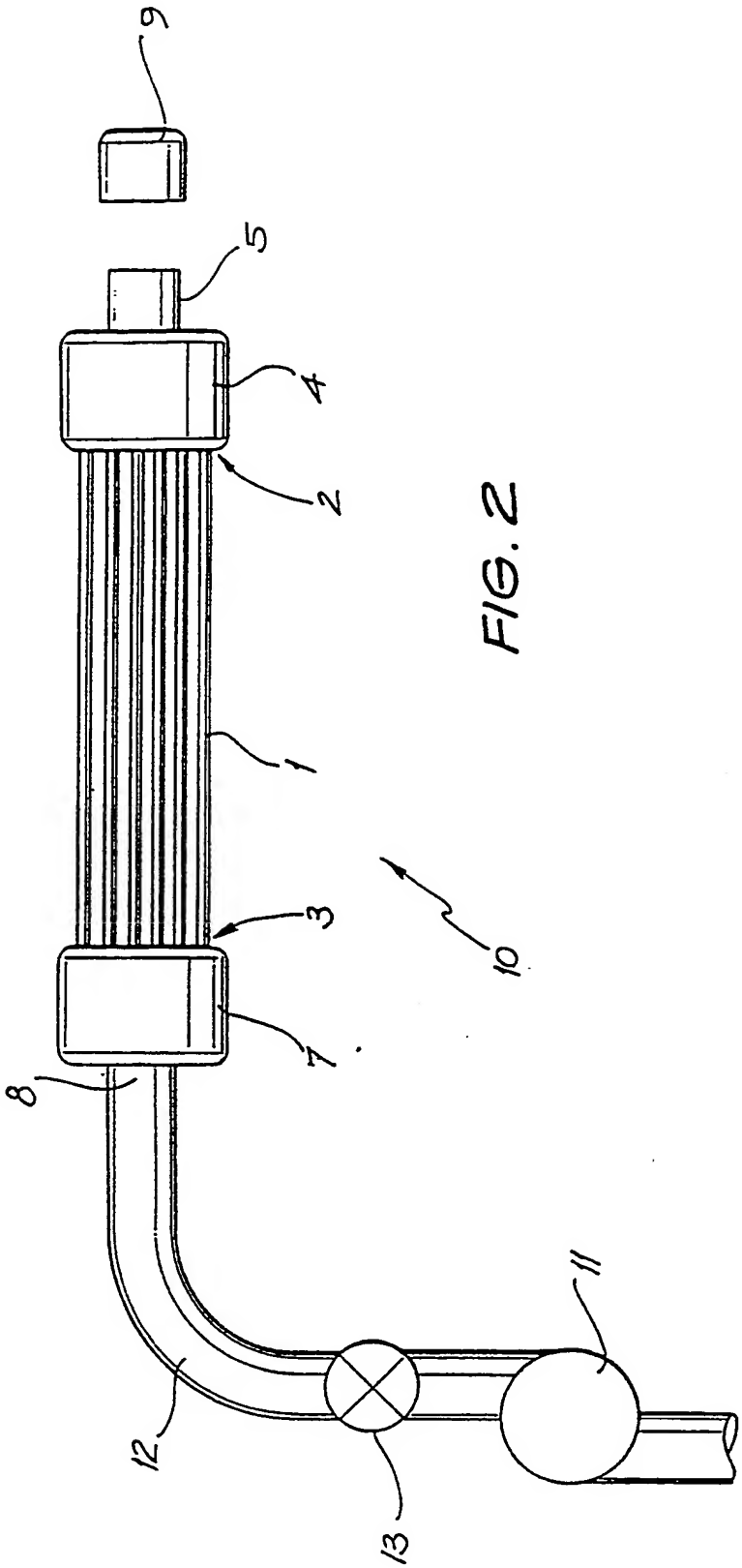

FIG. 2

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 6

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[5] A61M 31/00, A61D 7/00, A61F 2/02, C12N 5/08

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
IPC	A61M 31/00, A61F 1/00, 2/02

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched 8

AU: IPC as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT 9

Category*	Citation of Document, [11] with indication, where appropriate, of the relevant passages 12	Relevant to Claim No 13
X	EP,A, 0147939 (JOHNSON & JOHNSON) 10 July 1985 (10.07.85) See pages 7-8	(1-8,41,43,45, 48-49)
X,Y	GB,A, 2185408 (RHODE ISLAND HOSPITAL) 22 July 1987 (22.07.87) See columns 1-2	(1-4,9-10,13-15, 17-26,29-31,36, 40-45,49-59)
X,Y,A	WO,A, 89/04655 (BROWN UNIVERSITY RESEARCH FOUNDATION) 1 June 1989 (01.06.89) See pages 5-13	(1-4,9-10,13-15, 17-26,29-31,34-39 41,43,45,49-59)
Y	WO,A, 84/01287 (SPIELBERG) 12 April 1984 (12.04.84) See pages 2-4	(1-8)
	(continued)	

* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
5 September 1990 (05.09.90)	13 September 1990
International Searching Authority	**Signature of Authorized Officer**
Australian Patent Office	A HENDRICKSON

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

Y	AU,B, 61749/86 (HANA BIOLOGICS INC) 5 March 1987 (05.03.87) See pages 1-12, 19,26	(1-11,13,15,18-27, 29,31,36,39-41 43,45,48-51,53 56-59)
Y	US,A, 3625198 (SPARKS) 7 December 1971 (07.12.71) See column 2, lines 36-53	(39)
A	EP,A, 0161640 (MERCK AND CO INC) 21 November 1985 (21.11.85) See pages 1,6,9-13	(1,17,39,41-45, 47-55)

V. [] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 1

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.[] Claim numbers ..., because they relate to subject matter not required to be searched by this Authority, namely:

2.[] Claim numbers .., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3.[] Claim numbers ...., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4 (a):

VI. [] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2

This International Searching Authority found multiple inventions in this international application as follows:

1.[ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2.[ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3.[ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4.[ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON
INTERNATIONAL APPLICATION NO. PCT/AU 90/00281

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Members		
WO 8904655	AU 27184/88	DK 1216/90	FI 902427
	NO 902195	US 4892538	
US 3625198	CH 530787	DE 2022576	DE 2065370
	DE 2065440	FR 2047537	GB 1319641
	GB 1319642	US 3707958	US 3710400
	US 3806573	US 3866247	US 3866609
	CA 973651	DE 1766712	FR 1575107
	GB 1243375	US 3514791	US 3703009
	CA 985853	CH 562606	DE 2159666
	FR 2119319	GB 1330192	IT 965575
	US 3710777	US 3938524	
GB 2185408	CA 1272422	DE 3701148	FR 2592785
	JP 62211062	NL 8700097	
AU 61749/86	EP 213908	JP 62079065	US 4902295
WO 8401287	EP 120061		
EP 147939	AU 35426/84	JP 60123422	
EP 161640	AU 42408/85	JP 60246317	US 4686098
	ZA 8503584		